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Small molecule epigenetic modifiers combined with cell signalling modulators as a promising cell reprogramming strategy

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Abstract:

Recent achievements of cellular reprogramming have enabled the generation of induced pluripotent stem cells or other lineage-committed cells from more accessible and abundant somatic cell types by defined genetic factors. However, serious concerns remain about the efficiency and safety of current genetic approaches.

Recent studies showed that cell reprogramming can also be achieved purely by chemical approach (small molecule approach). Generation of induced pluripotent cells or trans-differentiation of one cell type to another had been achieved by biologically active small molecules that are involved in the regulation of the modulators of epigenetic machinery and specific cell signaling pathways.

Recently, using this cell reprogramming strategy we have been able to turn human mesenchymal stem cells directly into neuronal progenitors that have the potential to generate different neuronal subtypes, such as dopaminergic, cholinergic, and GABAergic cells when further grown in appropriate neuronal differentiation media (Fig.1).

We also demonstrated that this approach can be used to manipulate the fate of Cancer cells. Our studies showed that glioblastoma cell completely eradicated when exposed to specific combinations of epigenetic modulators (Fig.2). Interestingly, small percentage of glioblastoma cells differentiated into neuronal-like cells when epigenetic modifiers combined with specific modulators of cell signaling pathways that promote neural differentiation.

Conclusion

All these data (ours and others) suggest that the specific combinations of epigenetic modifiers can reactivate or enhance the plasticity of adult somatic cells (stem/progenitor cells or mature differentiated cells) which at appropriate environmental signals can be converted into more immature cell stages with wider differentiation potential or directly turned into other cell types. These data also showed, that similar to the normal somatic cells, cancer cells fate can also be changed with similar cell reprogramming approach. With further advances in understanding the major mechanisms in epigenetic regulation and development of new specific chemical tools for their regulation will open new exciting perspectives not only for regenerative medicine but also for cancer treatments.

Keywords:

cell reprogramming, epigenetic, small molecules, neural, dedifferentiation, transdifferentiation, differentiation

Relevant Image:

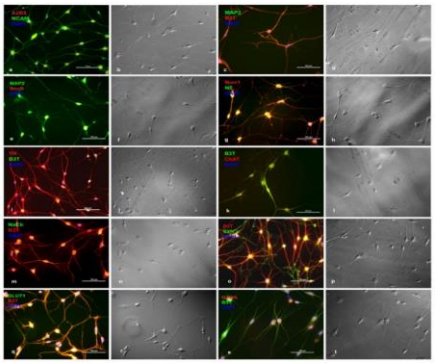

Fig.1.Morphological and immunocytochemical characterization of neutrally modified MSCs.

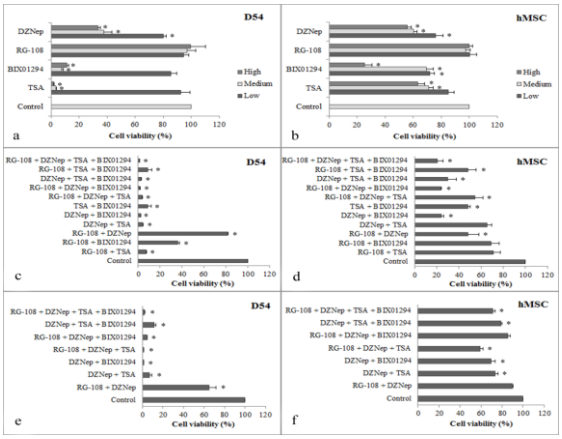

Fig.2. Cell viability assay for D54 (a) and hMSCs (b) treated with low, medium and high concentrations of epigenetic modifiers DZNep, RG-108, BIX01294 and TSA. Cell viability assay for D54 (c) and hMSCs (d) treated with different combinations of low and medium concentrations of epigenetic modifiers (low for DZNep and RG100 and medium for BIX01294 and TSA). Cell viability assay for D54 (e) and hMSCs (f) treated with different combinations of low concentrations of epigenetic modifiers DZNep, RG-108, BIX01294 and TSA. *: comparison of treated samples with control, +: comparison of the effect of high and medium concentrations with low concentration of epigenetic modifier. $P \leq 0.05$ were considered significant.

Biography:

Alexanian Arshak is currently the Chief Scientific Officer at Cell Reprogramming & Therapeutics LLC and an Adjunct Associate Professor in the Department of Medicine at the Medical College of Wisconsin (MCW). Previously, he held faculty positions in the Departments of Neurosurgery at MCW (2000-2013) and in the Departments of Anatomy and Neurobiology, as well as in Biochemistry and Molecular Biology, at Colorado State University (1997-2000). He has received training at universities and centers worldwide, including the Pasteur Institute and University of Montpelier in France, University of Saarland in Germany, Institute of Biochemistry in China and Russia, and Colorado State University. His research funded by the governmental grants such as NIH and Veterans Affairs, as well as other organizations such as Spinal Cord Society, Quadracci, Bryon Riesch Paralysis Foundation, AOSpine North America and International, Hansjorg Wyss and others. The areas of interest of his research are the epigenetic regulation of cell fate commitment and differentiation, development of cell reprogramming technologies to produce different neuronal and glial cell types, and elucidation of the therapeutic effect of these specialized cell types in several neurological disorders.

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